hybridised against female human genomic DNA to a high resolution array-Comparative Genomic Hybridisation (aCGH) platform containing ~43,000 probes (Agilent 44K Human Whole-Genome 44B arrays). Genomic regions with significant copy-number variation (CNV) (DNA gain/loss) were identified using an aberration detection algorithm (CGH Analytics V3.4).

Results: The most frequent CNVs in current smokers were gain of 1q21.1-q24.2 and 5p15.33-p12 (>60% of tumours) and loss of 8p23.3-p12 and 13q12.11-q34 (>20% of tumours). The most frequent CNVs in former smokers were gain at 1q25.2-q44 and 17q11.2-q25.3 (>50% of tumours) and loss at 13q12.11-q21.2 and 21q11.2-q22.3 (>20% of tumours). The most frequent CNVs in never smokers were gain at 7p22.3-p11.2 (>50% of tumours) and loss at 8p23.3-p11.22 and 13q13.3-q14.3 (>50% of tumours). CNVs present in both current and former smokers were compared to identify recurrent (occurring in >30% of tumours, both smokers and former smokers) genomic aberrations. Frequent copy-number gain was observed at 1q21.1-q31.3, 1q31.1-q44, 3q26.1-q29, 5p15.33-p12, 7p22.1-p11.2, 7p11.1-q36.2, and 17q21.2-q25.3. Gain at 1q25.2-q31.3 occurred in more than 50% of current and former smokers, yet was rarely gained in never-smokers (8%).

Conclusions: In the chaos that occurs in lung cancer cells that develop in current smokers (with continued carcinogenic exposure and therefore high lung cancer risk), those aberrations in common with lung cancer cells that develop in former smokers (with no further carcinogenic exposure and therefore lower but persistent lung cancer risk) may represent irreversible causative genetic damage. Genes located in these aberrations represent strong chemoprevention targets. Our analysis has identified several loci frequently aberrant in both current and former smokers. These loci are now being further studied to identify the potential gene targets of aberration.

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Session A7: Prevention & Early Detection

Monday, September 3

A7-01 **Prevention & Early Detection, Mon, 13:45 - 15:30**

The Danish randomized lung cancer CT screening trial. Results at baseline

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Objective: The Danish lung cancer screening trial is a randomized trial comparing CT screening with no screening. The trial is done with the NELSON trial in the Netherlands, Europe. The final end point is lung cancer mortality.

Methods: From 2004 to 2006 4104 Danish smokers and previous smokers were randomized to either screening with annual low dose CT scans for 5 years or no screening. A history of cigarette smoking of at least 20 pack years was required. All had lung function tests, and questionnaires regarding psychosocial consequences of screening, smoking and smoking cessation at randomization and planned annually.

All scans are performed with a 16 detector row CT scanner at low dose levels, and viewed independently by two board certified radiologists. Nodules identified in the baseline year were considered prevalence nodules.

Nodules were classified according to size and other characteristic:

- Nodules smaller than 5 mm and calcified nodules with a maximal diameter up to 20 mm were just tabulated.
- Uncalcified nodules with a diameter between 5 and 15 mm were re-scanned after 3 months; 1) if the size was stable or reduced no further action was taken.2) If the nodule grew it was referred for invasive workup, as were uncalcified nodules larger than 15 mm.

CT with contrast and PET CT was performed before any invasive procedures.

Results: At baseline 177 persons had nodules larger than 5 mm on the first scan, and almost all were rescanned after 3 months.

- Seventeen individuals (0.8%) with a suspicious lung nodule were referred to surgical exploration and all turned out to have cancer. One stage IA patient had segmental resection (adenocarcinoma (ACL) dominated by BAC features), ten patients (6 stage IA, 3 stage IB and 1 stage IIIB) had lobectomy (9 ACL and 1 squamous cell carcinoma (SQC), one stage IIIA had pneumonectomy (ACL).The remaining five patients were in stage IIIA after diagnostic evaluation and received chemotherapy (3 non small cell lung carcer (NSCLC), probably ACL, 1 ACL, 1 SQC).
- Seventy one percent had ACL, 12% SQC and 17% NSCLC. No SCLC was diagnosed.
- Twelve of 17 lung cancers at base line were treated surgically, 8 of these were treated by VATS resection.
- One participant had a benign hamartoma (4 cm) removed by VATS local resection and one had a diagnostic VATS on suspicion of mesothelioma which turned out to be pleural tuberculosis.
- Rate of false positive diagnoses was 8,6 %.
- In the control group so far one patient had a lobectomy (ACL) stage 1, one had a pneumonectomy for a stage IIIA lung cancer, two had oncological treatment for stage 4 disease (ACL) and one patient died with lung cancer stage IIIB (ACL).

Conclusion: Screening facilitates minimal invasive treatment and can be performed with a low rate of false positive diagnoses.

A7-02 **Prevention & Early Detection, Mon, 13:45 - 15:30**

Identification of polymorphisms in the Caspase-3 gene and their association with lung cancer risk

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Background: Caspase-3 (CASP-3) is a primary effector CASP that executes programmed cell death, and it plays an important role in the development and progression of cancer. Polymorphisms in the CASP-3 gene may influence CASP-3 production and/or activity, thereby modulating the susceptibility to lung cancer. To test this hypothesis, we investigated the association between CASP-3 polymorphisms and the risk of lung cancer in a Korean population.

Methods: We first screened single nucleotide polymorphisms (SNPs) in the CASP-3 gene by direct sequencing of genomic DNA samples taken from 27 healthy Korean individuals. We selected identified SNPs based on their frequency, linkage disequilibrium (LD) status and haplotype tagging status, and then genotyped the selected SNPs in 582 lung cancer patients and 582 healthy controls who were frequency matched for age and gender.

Results: We identified eight SNPs: six known SNPs (-928A>G, 246C>T, 829C>A, 1143G>C, 17532A>C and 20541C>T); and two novel SNPs (77G>A and 163G>T). Individuals with at least one variant allele of the -928A>G, 77G>A and 17532A>C polymorphisms were at a significantly decreased risk for lung cancer in comparison to the carriers with each homozygous wild-type allele [adjusted odds ratio (OR) = 0.79, 95% confidence interval (CI) = 0.62-1.00, P = 0.05; adjusted OR = 0.78, 95% CI = 0.61-0.99, P = 0.04; and adjusted OR = 0.74, 95% CI = 0.58-0.95, P = 0.02, respectively). Consistent with the results of genotyping analysis, the GAGC haplotype carrying the variant allele at all of the -928A>G, 77G>A, and 17532A>C loci was associated with a significantly decreased risk of lung cancer compared to the AGGA haplotype carrying no variant alleles at the three loci (adjusted OR = 0.66, 95% CI = 0.51-0.86, P = 0.002 and Bonferroni corrected P = 0.008).

Conclusions: These results suggest that the CASP-3 polymorphisms and their haplotypes contribute to the genetic susceptibility to lung cancer.

A7-03 **Prevention & Early Detection, Mon, 13:45 - 15:30**

Sputum cytometry to detect lung cancer

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Background: Improved early detection remains the most promising method of improving patient survival from lung cancer, and is a realistic goal in the short term. This study reports the findings of a large scale trial evaluating a novel, fully automated method of DNA cytometry on sputum to detect lung cancer.

Methods: Over a period of 18 months, 1235 patients clinically suspicious of having lung cancer were recruited into a multinational validation trial of the LungSign™ sputum test. Induced sputum was collected at the time of initial presentation, fixed and treated with dithiothreitol (DTT). Papanicolaou stained smears were prepared and analysed by conventional cytology. Monolayer cytospin slides were prepared and stained using the Feulgen-thionin method. Cytospin slides were scored using LungSign, a test that uses a fully automated computerised DNA cytometry system to analyze thousands of epithelial cell nuclei to generate a measure associated with malignancy.

Results: Of the 1123 patients analysed, 370 proved to have lung cancer (prevalence 33%). The LungSign test provided an ROC "area under the curve" value of 0.692, and for a specificity of 91% it detected 40% of all lung cancers (Figure 1). Results were similar for all lung cancer histological types, as well as early (up to 1b) and later (stage 2a and above) stages. Conventional cytology detected 16% of cancers with a specificity of 99%. Approximately 12% of cytospins contained insufficient epithelial cells for cytometric analysis. The inadequacy rate for conventional cytology was 43%.

Conclusions: In a high risk population, the LungSign test provides an effective means of detecting those patients most likely to have lung cancer. It is a continuous measure, permitting different cut points to be set. This flexibility allows the test to be used in multiple contexts such as screening patients for lung cancer or evaluating suspicious lesions detected on CT, thereby directing efficient use of other, more expensive and invasive diagnostic modalities.

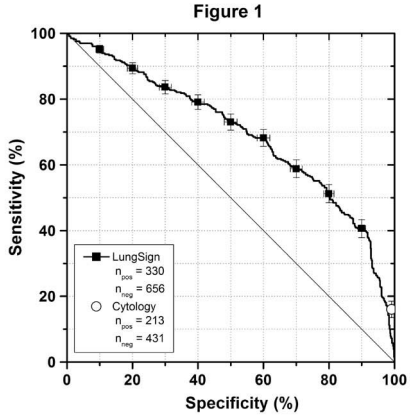

Figure 1; ROC curve for the LungSign score, with conventional cytology (circle). Sensitivity and specificity standard error bars representing one standard deviation are shown.

A7-04 **Prevention & Early Detection, Mon, 13:45 - 15:30**

Update on the use of oral iloprost for the chemoprevention of lung cancer

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Background: Pre-clinical studies have shown that the majority of NSCLC have decreased expression of prostacyclin synthase (PGIS) and genetically modified mice with selective pulmonary PGIS overexpression are chemoprevented from developing lung cancer in a variety of models, including cigarette smoke exposure. Based on these promising results, a multi-center, double-blind, placebo controlled, phase II trial of iloprost (an oral prostacyclin analogue) in subjects at increased risk for lung cancer was initiated and continues to enroll.

Methods: Subjects are selected for the trial if they meet the following criteria: current or former smoker (> 20 pack years); at least mild cytologic atypia on sputum cytology; no previous history of cancer. Fluorescent bronchoscopy is then performed with 6 standard sites biopsied, along with all other abnormally appearing areas. Subjects are then randomized to iloprost (in escalating doses) or placebo for 6 months and then undergo a repeat fluorescent bronchoscopy with repeat biopsy of all the central airway areas sampled on the first bronchoscopy. The primary endpoints for the study are bronchial histology and Ki-67